Orally-Bioavailable Formulations of Fentanyl and Congeners Thereof

Related Applications

This application claims the benefit of priority to United States Provisional Patent Application serial number 60/251,144, filed December 4, 2000.

Background of the Invention

Pain is an unpleasant sensation varying in severity in a local part of the body or several parts of the body resulting from injury, disease, or emotional disorder. Pain can be classified according to its duration. Acute pain, which lasts less than one month, usually has a readily identifiable cause and signals tissue damage. In addition, acute pain syndromes can be episodic, for example recurrent discomfort from arthritis. Chronic pain can be defined as pain that persists more than one month beyond the usual course of an acute illness or injury, or pain that recurs at intervals over months or years, or pain that is associated with a chronic pathologic process. In contrast to acute pain, chronic pain loses its adaptive biologic function. Depression is common, and abnormal illness behavior often compounds the patient's impairment.

Millions of people suffer from chronic or intractable pain. Persistent pain varies in etiology and presentation. In some cases, symptoms and signs may be evident within a few weeks to a few months after the occurrence of an injury or the onset of disease, e.g. cancer or AIDS. Like many illnesses that at one time were not well understood, pain and its many manifestations may be poorly treated and seriously underestimated. Inappropriately treated pain seriously compromises the patient's quality of life, causing emotional suffering and increasing the risk of lost livelihood and disrupted social integration. Severe chronic pain affects both the pediatric and adult population, and often leads to mood disorders, including depression and, in rare cases, suicide.

In the last several years, health policy-makers, health professionals, regulators, and the public have become increasingly interested in the provision of better pain therapies. This interest is evidenced, in part, by the U.S. Department of Health and

Human Services' dissemination of Clinical Practice Guidelines for the management of acute pain and cancer pain. There is currently no nationally accepted consensus for the treatment of chronic pain not due to cancer, yet the economic and social costs of chronic pain are substantial, with estimates ranging in the tens of billions of dollars annually.

Three general classes of drugs are currently available for pain management, nonsteriodal anti-inflammatories, opioids, and adjuvant analgesics. The nonsteriodal anti-inflammatories class includes drugs such as aspirin, ibuprofen, diclofenac, acetaminophen, celecoxib, and rofecoxib. The opioid class includes morphine, oxycodone, fentanyl, and pentazocine. Adjuvant analgesics include various antidepressants, anticonvulsants, neuroleptics, and corticosteroids.

Opioids are the major class of analgesics used in the management of moderate to severe pain because of their effectiveness, ease of titration, and favorable risk-to-benefit ratio. Opioids produce analgesia by binding to specific receptors both within and outside the CNS. Opioid analgesics are classified as full agonists, partial agonists, or mixed agonist-antagonists, depending on the receptors to which they bind and their intrinsic activities at each receptor.

Three subclasses of opioid receptor have been identified in humans, namely the δ-, κ-, and μ-opioid receptors. Analgesia is thought to involve activation of μ and/or κ receptors. Notwithstanding their low selectivity for μ over κ receptors, it is likely that morphine and morphine-like opioid agonists produce analgesia primarily through interaction with μ receptors; selective agonists of κ receptors in humans produce analgesia, because rather than the euphoria associated with morphine and congeners, these compounds often produce dysphoria and psychotomimetic effects. The consequences of activating δ receptors in humans remain unclear.

Although opioids can be very effective in pain management, they do cause several side effects, such as respiratory depression, constipation, physical dependence, tolerance, withdraw. These unwanted effects can severely limit their use.

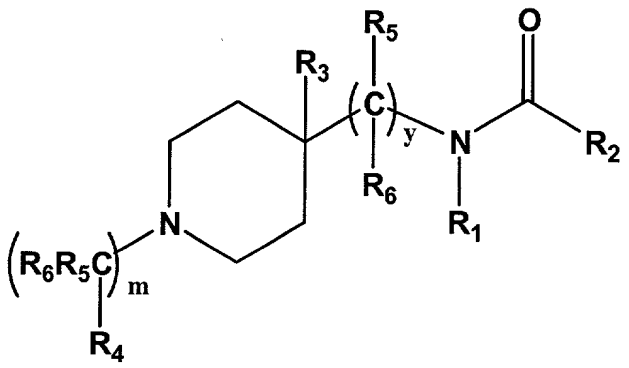
Commonly used full agonists include morphine, hydromorphone, meperidine, methadone, levorphanol, and fentanyl. These opioids are classified as full agonists

because there is not a ceiling to their analgesic efficacy, nor will they reverse or antagonize the effects of other opioids within this class when given simultaneously. Side effects include respiratory depression, constipation, nausea, urinary retention, confusion, and sedation. Morphine is the most commonly used opioid for moderate to severe pain because of its availability in a wide variety of dosage forms, its well-characterized pharmacokinetics and pharmacodynamics, and its relatively low cost. Meperidine may be useful for brief courses (e.g., a few days) to treat acute pain and to manage rigors (shivering) induced by medication, but it generally should be avoided in patients with cancer because of its short duration of action (2.5 to 3.5 hours) and its toxic metabolite, normeperidine. This metabolite accumulates, particularly when renal function is impaired, and causes CNS stimulation, which may lead to dysphoria, agitation, and seizures; meperidine, therefore, should not be used if continued opioid use is anticipated.

Drug delivery takes a variety of forms, depending on the agent to be delivered and the administration route. The most convenient way to administer drugs into the body is by oral administration. However, many drugs, including fentanyl and its congeners, are poorly absorbed and unstable during passage through the gastrointestinal (G-I) tract. The administration of these drugs is generally performed through injection. Controlled release systems for drug delivery are often designed to administer drugs to specific areas of the body. In the gastrointestinal tract it is important that the drug not be eliminated before it has had a chance to exert a localized effect or to pass into the bloodstream.

Summary of the Invention

One aspect of the present invention relates to a formulation, comprising: an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, and polymeric carriers; and a compound represented by **A**:



A

wherein

m is 0, 1, 2, 3 or 4;

y is 0, 1, or 2;

R_1 represents alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

R_2 represents H, alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

R_3 represents H, alkyl, aryl, heteroaryl, OR_2, $OC(O)R_2$, CH_2OR_2, or CO_2R_2;

R_4 represents H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, or heteroaryl;

R_5 represents independently for each occurrence H, alkyl, cycloalkyl, aryl, heteroaryl, F, OR_2, or $OC(O)R_2$;

R_6 represents independently for each occurrence H, alkyl, cycloalkyl, aryl, heteroaryl, F, OR_2, or $OC(O)R_2$;

any two geminal or vicinal instances of R_5 and R_6 may be connected through a covalent bond; and

the stereochemical configuration at any stereocenter of a compound represented by **A** is *R, S*, or a mixture of these configurations.

In certain embodiments of the formulation of the present invention, the excipient is a cyclodextrin.

In certain embodiments of the formulation of the present invention, m is 2 or 3. In certain embodiments of the formulation of the present invention, m is 2. In certain embodiments of the formulation of the present invention, y is 0. In certain embodiments of the formulation of the present invention, R_1 represents aryl or heteroaryl. In certain embodiments of the formulation of the present invention, R_1 represents aryl. In certain

embodiments of the formulation of the present invention, R_2 represents independently for each occurrence alkyl. In certain embodiments of the formulation of the present invention, R_3 represents H or alkyl. In certain embodiments of the formulation of the present invention, R_3 represents H. In certain embodiments of the formulation of the present invention, R_4 represents cycloalkyl, aryl, or heteroaryl. In certain embodiments of the formulation of the present invention, R_4 represents aryl. In certain embodiments of the formulation of the present invention, R_5 represents independently for each occurrence H, or alkyl. In certain embodiments of the formulation of the present invention, R_5 represents independently for each occurrence H. In certain embodiments of the formulation of the present invention, R_6 represents independently for each occurrence H, or alkyl. In certain embodiments of the formulation of the present invention, R_6 represents independently for each occurrence H.

In certain embodiments of the formulation of the present invention, m is 2; and y is 0. In certain embodiments of the formulation of the present invention, m is 2; y is 0; and R_1 represents aryl. In certain embodiments of the formulation of the present invention, m is 2; y is 0; and R_1 represents aryl. In certain embodiments of the formulation of the present invention, m is 2; y is 0; R_1 represents aryl; and R_2 represents independently for each occurrence alkyl. In certain embodiments of the formulation of the present invention, m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; and R_3 represents H. In certain embodiments of the formulation of the present invention, m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; and R_4 represents aryl. In certain embodiments of the formulation of the present invention, m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; R_4 represents aryl; and R_5 represents independently for each occurrence H. In certain embodiments of the formulation of the present invention, m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; R_4 represents aryl; R_5 represents independently for each occurrence H; and R_6 represents independently for each occurrence H. In certain embodiments of the formulation of the present invention, m is 2; y is 0; R_1 represents phenyl; R_2 represents independently for each occurrence ethyl; R_3 represents H; R_4 represents phenyl; R_5 represents independently for each occurrence H;

and R_6 represents independently for each occurrence H.

Another aspect of the present invention relates to a method of treating pain, drug addiction, or tinnitus in a mammal, comprising the step of administering to a mammal in need thereof an effective amount of a formulation of the present invention. In certain embodiments of the method of the present invention, said mammal is a primate, equine, canine or feline. In certain embodiments of the method of the present invention, said mammal is a human. In certain embodiments of the method of the present invention, said formulation is administered orally.

Detailed Description of the Invention

Pain is an unpleasant sensation varying in severity in a local part of the body or several parts of the body resulting from injury, disease, or emotional disorder. Pain can be classified according to its duration. Acute pain, which lasts less than one month, usually has a readily identifiable cause (e.g., hip fracture) and signals tissue damage. The associated effect is often anxiety, and the concomitant physiologic findings are those of sympathetic stimulation (e.g., tachycardia, tachypnea, diaphoresis). In addition, acute pain syndromes can be episodic, for example recurrent discomfort from arthritis.

Chronic pain can be defined as pain that persists more than one month beyond the usual course of an acute illness or injury, or pain that recurs at intervals over months or years, or pain that is associated with a chronic pathologic process. In contrast to acute pain, chronic pain loses its adaptive biologic function. Depression is common, and abnormal illness behavior often compounds the patient's impairment. Chronic pain can be divided broadly into that which is inferred to be predominantly somatogenic and that which is inferred to be predominantly psychogenic. A similar classification based on inferred pathophysiology designates chronic pain as nociceptive (commensurate with ongoing activation of pain-sensitive nerve fibers), neuropathic (due to aberrant somatosensory processing in afferent neural pathways), or psychogenic.

Nociceptive pain can be somatic or visceral. Most chronic pain in the elderly is nociceptive and somatic; arthritis, cancer pain, and myofascial pain are most common. Relief is likely with removal of the peripheral cause (e.g., reducing periarticular inflammation), and analgesic drugs are often effective.

A common subtype of neuropathic pain, known collectively as peripheral neuropathic pain, is presumably sustained by mechanisms that involve disturbances in the peripheral nerve or nerve root; neuroma formation after axonal injury and nerve compression are the two major processes. Another subtype of neuropathic pain is related to the reorganization of nociceptive information processing by the CNS; it persists without ongoing activation of pain-sensitive fibers. This type of pain, known collectively as the deafferentation syndromes, includes postherpetic neuralgia, central pain (which can result from a lesion at any level of the CNS), phantom limb pain, and others. A third subtype of neuropathic pain, often called sympathetically maintained pain, can be ameliorated by interruption of sympathetic nerves to the painful area; the prototypic disorder is reflex sympathetic dystrophy. The precise mechanisms involved in these disorders are conjectural, but all can produce an unfamiliar pain, often described as burning and stabbing. Currently, this type of pain responds poorly to analgesics.

Some patients have persistent pain without either nociceptive foci or evidence of a neuropathic mechanism for the pain. Many others have nociceptive lesions that do not sufficiently explain the degree of pain and disability. Psychopathologic processes account for these complaints in some patients. If no evidence for a psychological cause is found, the pain is referred to as idiopathic. Many patients have an idiopathic pain syndrome that is best described by the generic diagnosis chronic nonmalignant pain syndrome, a term denoting pain and disability disproportionate to an identifiable somatic cause and usually related to a more pervasive set of abnormal illness behaviors. Some of these patients may be labeled by the more formal psychiatric diagnosis of somatoform pain disorder. Others have complaints that constitute a specific pain diagnosis, most commonly the failed low back syndrome or atypical facial pain. Still others have significant organic lesions (e.g., lumbar arachnoiditis) but also have a clear psychological contribution associated with excessive disability. Diagnosis may be difficult, but the relative contributions of both organic and psychological components of the pain can be defined.

Another clinically useful classification of chronic pain is broadly syndromic. For example, chronic pain may be part of a medical illness (e.g., cancer or arthritis). A mixture of pathophysiologic mechanisms may be involved; e.g., tumor invasion of nerve

and bone may cause neuropathic and somatic nociceptive pains, respectively, and psychological factors may be prominent.

Three general classes of drugs are currently available for pain management, nonsteriodal anti-inflammatories, opioids, and adjuvant analgesics. The nonsteriodal anti-inflammatories class includes drugs such as aspirin, ibuprofen, diclofenac, acetaminophen, and rofecoxib. The opioid class includes morphine, oxycodone, fentanyl, and pentazocine. Adjuvant analgesics include various antidepressants, anticonvulsants, neuroleptics, and corticosteroids.

Of the three classes of pharmaceutical agents used for pain management, opioid are usually most efficacious for treating moderate to severe pain. Although opioids can be very effective in pain management, they do cause several side effects, such as respiratory depression, constipation, physical dependence, tolerance, withdraw. These unwanted effects can severely limit their use. Therefore, there is a current need for pharmaceutical agents that retain the analgesic properties of the known opioid, but have reduced side effect profiles for the treatment of pain.

Opioids, specifically ligands for the μ-opioid receptor, are the major class of analgesics used in the management of moderate to severe pain because of their effectiveness, ease of titration, and favorable risk-to-benefit ratio. Unfortunately, the opioids currently available have several unwanted side-effects, such as respiratory depression and constipation. In addition, these agents may lead to tolerance and dependence. Research into the development of new, selective ligands for opioid receptors holds the promise of yielding potent analgesics that lack the side effects of morphine and its congeners. Applicants herein disclose novel analgesics, including selective ligands for opioid receptors. Individual compounds described herein promise to have agonistic, antagonistic, and hybrid effects on opioid and other cellular receptors. Additionally, new compounds reported herein may possess analgesic properties free from respiratory depression and the potential for physical dependence associated with μ-opioid receptor ligands, such as morphine and fentanyl. Moreover, new compounds reported herein may possess properties for the treatment of physical or psychological additions, psychiatric disorders, and neurological pathologies, such as tinnitus.

One aspect of the present invention relates to orally bioavailable formulations of fentanyl and its congeners, comprising a compound selected from the group consisting of fentanyl and its congeners; and an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, and polymeric carriers. Each of these classes of excipients is discussed below or in the section entitled "Pharmaceutical Formulations" or both.

Micelles

Recently, the pharmaceutical industry introduced microemulsification technology to improve bioavailability of some lipophilic (water insoluble) pharmaceutical agents. Examples include Trimetrine (Dordunoo, S. K., et al., Drug Development and Industrial Pharmacy, 17(12), 1685-1713, 1991 and REV 5901 (Sheen, P. C., et al., J Pharm Sci 80(7), 712-714, 1991). Among other things, microemulsification provides enhanced bioavailability by preferentially directing absorption to the lymphatic system instead of the circulatory system, which thereby bypasses the liver, and prevents destruction of the compounds in the hepatobiliary circulation.

In one aspect of invention, the formulations contain micelles formed from fentanyl and at least one amphiphilic carrier, in which the micelles have an average diameter of less than about 100 nm. More preferred embodiments provide micelles having an average diameter less than about 50 nm, and even more preferred embodiments provide micelles having an average diameter less than about 30 nm, or even less than about 20 nm.

While all suitable amphiphilic carriers are contemplated, the presently preferred carriers are generally those that have Generally-Recognized-as-Safe (GRAS) status, and that can both solubilize fentanyl and microemulsify it at a later stage when the fentanyl solution comes into a contact with a complex water phase (such as one found in human gastro-intestinal tract). Usually, amphiphilic ingredients that satisfy these requirements have HLB (hydrophilic to lipophilic balance) values of 2-20, and their structures contain straight chain aliphatic radicals in the range of C-6 to C-20. Examples are polyethylene-glycolized fatty glycerides and polyethylene glycols.

Particularly preferred amphiphilic carriers are saturated and monounsaturated

polyethyleneglycolyzed fatty acid glycerides, such as those obtained from fully or partially hydrogenated various vegetable oils. Such oils may advantageously consist of tri-. di- and mono-fatty acid glycerides and di- and mono-polyethyleneglycol esters of the corresponding fatty acids, with a particularly preferred fatty acid composition including capric acid 4-10, capric acid 3-9, lauric acid 40-50, myristic acid 14-24, palmitic acid 4-14 and stearic acid 5-15%. Another useful class of amphiphilic carriers includes partially esterified sorbitan and/or sorbitol, with saturated or mono-unsaturated fatty acids (SPAN-series) or corresponding ethoxylated analogs (TWEEN-series).

Commercially available amphiphilic carriers are particularly contemplated, including Gelucire-series, Labrafil, Labrasol, or Lauroglycol (all manufactured and distributed by Gattefosse Corporation, Saint Priest, France), PEG-mono-oleate, PEG-di-oleate, PEG-mono-laurate and di-laurate, Lecithin, Polysorbate 80, etc (produced and distributed by a number of companies in USA and worldwide).

The emulsified formulations of fentanyl are expected to have better bioavailability after their oral administration than other fentanyl formulations presently available in the industry. Among other things, it is contemplated that the amphiphilic carriers will at least partially protect the fentanyl from being biotransformed in the gut or in the intestinal wall. It is also contemplated that the fentanyl-amphiphilic carrier complexes, in addition to being absorbed through the small intestinal wall, will be absorbed through the lymphatic system, and thereby avoid destruction in the hepatic biliary circulation.

Polymers

Hydrophilic polymers suitable for use in the present invention are those which are readily water-soluble, can be covalently attached to a vesicle-forming lipid, and which are tolerated in vivo without toxic effects (i.e., are biocompatible). Suitable polymers include polyethylene glycol (PEG), polylactic (also termed polylactide), polyglycolic acid (also termed polyglycolide), a polylactic-polyglycolic acid copolymer, and polyvinyl alcohol. Preferred polymers are those having a molecular weight of from about 100 or 120 daltons up to about 5,000 or 10,000 daltons, and more preferably from about 300 daltons to about 5,000 daltons. In a particularly preferred embodiment, the polymer is polyethyleneglycol having a molecular weight of from about 100 to about 5,000 daltons, and more preferably

having a molecular weight of from about 300 to about 5,000 daltons. In a particularly preferred embodiment, the polymer is polyethyleneglycol of 750 daltons (PEG(750)). Polymers may also be defined by the number of monomers therein; a preferred embodiment of the present invention utilizes polymers of at least about three monomers, such PEG polymers consisting of three monomers (approximately 150 daltons).

Other hydrophilic polymers which may be suitable for use in the present invention include polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses such as hydroxymethylcellulose or hydroxyethylcellulose.

In certain embodiments, a formulation of the present invention comprises a biocompatible polymer selected from the group consisting of polyamides, polycarbonates, polyalkylenes, polymers of acrylic and methacrylic esters, polyvinyl polymers, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, celluloses, polypropylene, polyethylenes, polystyrene, polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, proteins, polyhyaluronic acids, polycyanoacrylates, and blends, mixtures, or copolymers thereof.

Cyclodextrins

Cyclodextrins are cyclic oligosaccharides, consisting of 6, 7 or 8 glucose units, designated by the Greek letter .alpha., .beta. or .gamma., respectively. Cyclodextrins with fewer than six glucose units are not known to exist. The glucose units are linked by alpha-1,4-glucosidic bonds. As a consequence of the chair conformation of the sugar units, all secondary hydroxyl groups (at C-2, C-3) are located on one side of the ring, while all the primary hydroxyl groups at C-6 are situated on the other side. As a result, the external faces are hydrophilic, making the cyclodextrins water-soluble. In contrast, the cavities of the cyclodextrins are hydrophobic, since they are lined by the hydrogen of atoms C-3 and C-5, and by ether-like oxygens. These matrices allow complexation with a variety of relatively hydrophobic compounds, including, for instance, steroid compounds such as 17.beta.-estradiol (see, e.g., van Uden et al. Plant Cell Tiss. Org. Cult. 38:1-3-113 (1994)). The complexation takes place by Van der Waals interactions and by hydrogen

bond formation. For a general review of the chemistry of cyclodextrins, see, Wenz, Agnew. Chem. Int. Ed. Engl., 33:803-822 (1994).

The physico-chemical properties of the cyclodextrin derivatives depend strongly on the kind and the degree of substitution. For example, their solubility in water ranges from insoluble (e.g., triacetyl-beta-cyclodextrin) to 147% soluble (w/v) (G-2-beta-cyclodextrin). In addition, they are soluble in many organic solvents. The properties of the cyclodextrins enable the control over solubility of various formulation components by increasing or decreasing their solubility.

Numerous cyclodextrins and methods for their preparation have been described. For example, Parmeter (I), et al. (U.S. Pat. No. 3,453,259) and Gramera, et al. (U.S. Pat. No. 3,459,731) described electroneutral cyclodextrins. Other derivatives include cyclodextrins with cationic properties [Parmeter (II), U.S. Pat. No. 3,453,257], insoluble crosslinked cyclodextrins (Solms, U.S. Pat. No. 3,420,788), and cyclodextrins with anionic properties [Parmeter (III), U.S. Pat. No. 3,426,011]. Among the cyclodextrin derivatives with anionic properties, carboxylic acids, phosphorous acids, phosphinous acids, phosphonic acids, phosphoric acids, thiophosphonic acids, thiosulphinic acids, and sulfonic acids have been appended to the parent cyclodextrin [see, Parmeter (III), supra]. Furthermore, sulfoalkyl ether cyclodextrin derivatives have been described by Stella, et al. (U.S. Pat. No. 5,134,127).

Liposomes

Liposomes consist of at least one lipid bilayer membrane enclosing an aqueous internal compartment. Liposomes may be characterized by membrane type and by size. Small unilamellar vesicles (SUVs) have a single membrane and typically range between 0.02 and 0.05 μm in diameter; large unilamellar vesicles (LUVS) are typically larger than 0.05 μm Oligolamellar large vesicles and multilamellar vesicles have multiple, usually concentric, membrane layers and are typically larger than 0.1 μm. Liposomes with several nonconcentric membranes, i.e., several smaller vesicles contained within a larger vesicle, are termed multivesicular vesicles.

One aspect of the present invention relates to formulations comprising liposomes

containing fentanyl or congeners thereof, where the liposome membrane is formulated to provide a liposome with increased carrying capacity for fentanyl or one of its congeners. Alternatively or in addition, fentanyl or its congener may be contained within, or adsorbed onto, the liposome bilayer of the liposome. Fentanyl or its congener may be aggregated with a lipid surfactant and carried within the liposome's internal space; in these cases, the liposome membrane is formulated to resist the disruptive effects of the active agent-surfactant aggregate.

According to one embodiment of the present invention, the lipid bilayer of a liposome contains lipids derivatized with polyethylene glycol (PEG), such that the PEG chains extend from the inner surface of the lipid bilayer into the interior space encapsulated by the liposome, and extend from the exterior of the lipid bilayer into the surrounding environment.

Active agents contained within liposomes of the present invention are in solubilized form. Aggregates of surfactant and active agent (such as emulsions or micelles containing the active agent of interest) may be entrapped within the interior space of liposomes according to the present invention. A surfactant acts to disperse and solubilize the active agent, and may be selected from any suitable aliphatic, cycloaliphatic or aromatic surfactant, including but not limited to biocompatible lysophosphatidylcholines (LPCs) of varying chain lengths (for example, from about C.sub.14 to about C.sub.20). Polymer-derivatized lipids such as PEG-lipids may also be utilized for micelle formation as they will act to inhibit micelle/membrane fusion, and as the addition of a polymer to surfactant molecules decreases the CMC of the surfactant and aids in micelle formation. Preferred are surfactants with CMCs in the micromolar range; higher CMC surfactants may be utilized to prepare micelles entrapped within liposomes of the present invention, however, micelle surfactant monomers could affect liposome bilayer stability and would be a factor in designing a liposome of a desired stability.

Liposomes according to the present invention may be prepared by any of a variety of techniques that are known in the art. See, e.g., U.S. Pat. No. 4,235,871; Published PCT applications WO 96/14057; New RRC, Liposomes: A practical approach, IRL Press,

Oxford (1990), pages 33-104; Lasic DD, Liposomes from physics to applications, Elsevier Science Publishers BV, Amsterdam, 1993.

For example, liposomes of the present invention may be prepared by diffusing a lipid derivatized with a hydrophilic polymer into preformed liposomes, such as by exposing preformed liposomes to micelles composed of lipid-grafted polymers, at lipid concentrations corresponding to the final mole percent of derivatized lipid which is desired in the liposome. Liposomes containing a hydrophilic polymer can also be formed by homogenization, lipid-field hydration, or extrusion techniques, as are known in the art.

In another exemplary formulation procedure, the active agent is first dispersed by sonication in a lysophosphatidylcholine or other low CMC surfactant (including polymer grafted lipids) that readily solubilizes hydrophobic molecules. The resulting micellar suspension of active agent is then used to rehydrate a dried lipid sample that contains a suitable mole percent of polymer-grafted lipid, or cholesterol. The lipid and active agent suspension is then formed into liposomes using extrusion techniques as are known in the art, and the resulting liposomes separated from the unencapsulated solution by standard column separation.

In one aspect of the present invention, the liposomes are prepared to have substantially homogeneous sizes in a selected size range. One effective sizing method involves extruding an aqueous suspension of the liposomes through a series of polycarbonate membranes having a selected uniform pore size; the pore size of the membrane will correspond roughly with the largest sizes of liposomes produced by extrusion through that membrane. See e.g., U.S. Pat. No. 4,737,323 (Apr. 12, 1988).

Release Modifiers

The release characteristics of a formulation of the present invention depend on the encapsulating material, the concentration of encapsulated drug, and the presence of release modifiers. For example, release can be manipulated to be pH dependent, for example, using a pH sensitive coating that releases only at a low pH, as in the stomach, or a higher pH, as in the intestine. An enteric coating can be used to prevent release from occurring until after passage through the stomach. Multiple coatings or mixtures of cyanamide encapsulated in different materials can be used to obtain an initial release in

the stomach, followed by later release in the intestine. Release can also be manipulated by inclusion of salts or pore forming agents, which can increase water uptake or release of drug by diffusion from the capsule. Excipients which modify the solubility of the drug can also be used to control the release rate. Agents which enhance degradation of the matrix or release from the matrix can also be incorporated. They can be added to the drug, added as a separate phase (i.e., as particulates), or can be co-dissolved in the polymer phase depending on the compound. In all cases the amount should be between 0.1 and thirty percent (w/w polymer). Types of degradation enhancers include inorganic salts such as ammonium sulfate and ammonium chloride, organic acids such as citric acid, benzoic acid, and ascorbic acid, inorganic bases such as sodium carbonate, potassium carbonate, calcium carbonate, zinc carbonate, and zinc hydroxide, and organic bases such as protamine sulfate, spermine, choline, ethanolamine, diethanolamine, and triethanolamine and surfactants such as Tween.RTM. and Pluronic.RTM.. Pore forming agents which add microstructure to the matrices (i.e., water soluble compounds such as inorganic salts and sugars) are added as particulates. The range should be between one and thirty percent (w/w polymer).

Uptake can also be manipulated by altering residence time of the particles in the gut. This can be achieved, for example, by coating the particle with, or selecting as the encapsulating material, a mucosal adhesive polymer. Examples include most polymers with free carboxyl groups, such as chitosan, celluloses, and especially polyacrylates (as used herein, polyacrylates refers to polymers including acrylate groups and modified acrylate groups such as cyanoacrylates and methacrylates).

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The term "bioavailable" means that the therapeutically active medicament is absorbed from the formulation and becomes available in the body at the intended site of drug action.

The abbreviation "CNS" refers to the central nervous system of an organism.

The term "ED_{50}" means the dose of a drug which produces 50% of its maximum response or effect. Alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations.

The term "LD_{50}" means the dose of a drug which is lethal in 50% of test subjects.

The term "therapeutic index" refers to the therapeutic index of a drug defined as LD_{50}/ED_{50}.

The term "agonist" refers to a compound that mimics the action of natural transmitter or, when the natural transmitter is not known, causes changes at the receptor complex in the absence of other receptor ligands.

The terms "inverse agonist" and "negative antagonist" refer to compounds that are selective ligands for an inactive form of a cellular receptor which exists as an equilibrating mixture of active and inactive forms.

The term "antagonist" refers to a compound that binds to a receptor site, but does not cause any physiological changes unless another receptor ligand is present.

The term "competitive antagonist" refers to a compound that binds to a receptor site; its effects can be overcome by increased concentration of the agonist.

The term "partial agonist" refers to a compound that binds to a receptor site but does not produce the maximal effect regardless of its concentration.

The term "ligand" refers to a compound that binds at the receptor site.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

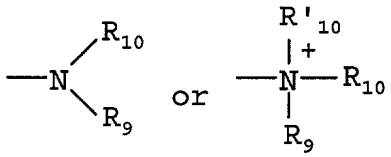
The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for example, azetidine, azepine, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

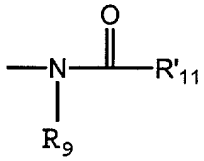
As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



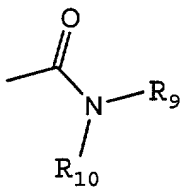
wherein R_9, R_{10} and R'_{10} each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R_8$, or R_9 and R_{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In preferred embodiments, only one of R_9 or R_{10} can be a carbonyl, e.g., R_9, R_{10} and the nitrogen together do not form an imide. In even more preferred embodiments, R_9 and R_{10} (and optionally R'_{10}) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_m-R_8$. Thus, the term "alkylamine" as used herein means an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R_9 and R_{10} is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R_9 is as defined above, and R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above.

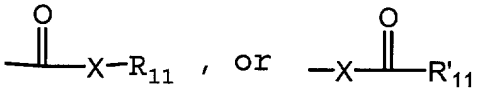
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R_9, R_{10} are as defined above. Preferred embodiments of the amide will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-$(CH_2)_m$-R_8, wherein m and R_8 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:

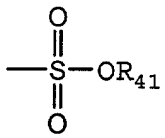


wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, an alkyl, an alkenyl, -$(CH_2)_m$-R_8 or a pharmaceutically acceptable salt, R'_{11} represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R_8, where m and R_8 are as defined above. Where X is an oxygen and R_{11} or R'_{11} is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R_{11} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and R'_{11} is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R_{11} or R'_{11} is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and R_{11} is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is a sulfur and R_{11}' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a

bond, and R_{11} is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R_{11} is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_m-R_8$, where m and R_8 are described above.

The term "sulfonate" is art recognized and includes a moiety that can be represented by the general formula:

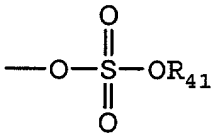


in which R_{41} is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

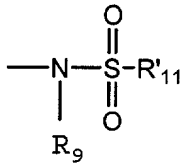
The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

The term "sulfate" is art recognized and includes a moiety that can be represented by the general formula:



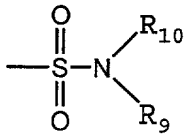
in which R_{41} is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that can be represented by the general formula:



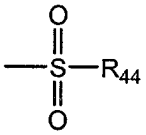
in which R_9 and R'_{11} are as defined above.

The term "sulfamoyl" is art-recognized and includes a moiety that can be represented by the general formula:



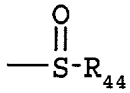
in which R_9 and R_{10} are as defined above.

The term "sulfonyl", as used herein, refers to a moiety that can be represented by the general formula:



in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

The term "sulfoxido" as used herein, refers to a moiety that can be represented by the general formula:



in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aralkyl, or aryl.

A "selenoalkyl" refers to an alkyl group having a substituted seleno group attached thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-$(CH_2)_m$-R_7, m and R_7 being defined above.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

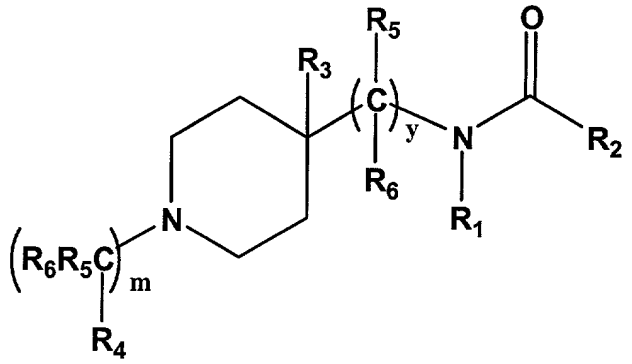
The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of

alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Formulations and Methods of the Invention

In certain embodiments, the present invention relates to a formulation, comprising: an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, and polymeric carriers; and a compound represented by **A**:



A

wherein

m is 0, 1, 2, 3 or 4;

y is 0, 1, or 2;

R_1 represents alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

R_2 represents H, alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

R_3 represents H, alkyl, aryl, heteroaryl, OR_2, $OC(O)R_2$, CH_2OR_2, or CO_2R_2;

R_4 represents H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, or heteroaryl;

R_5 represents independently for each occurrence H, alkyl, cycloalkyl, aryl, heteroaryl, F, OR_2, or $OC(O)R_2$;

R_6 represents independently for each occurrence H, alkyl, cycloalkyl, aryl, heteroaryl, F, OR_2, or $OC(O)R_2$;

any two geminal or vicinal instances of R_5 and R_6 may be connected through a covalent bond; and

the stereochemical configuration at any stereocenter of a compound represented by **A** is *R, S*, or a mixture of these configurations.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2 or 3.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein y is 0.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_1 represents aryl or heteroaryl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_1 represents aryl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_2 represents independently for each occurrence alkyl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_3 represents H or alkyl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_3 represents H.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_4 represents cycloalkyl, aryl, or heteroaryl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_4 represents aryl.

In certain embodiments, the formulations of the present invention comprise a

compound represented by **A** and the attendant definitions, wherein R_5 represents independently for each occurrence H, or alkyl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_5 represents independently for each occurrence H.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_6 represents independently for each occurrence H, or alkyl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein R_6 represents independently for each occurrence H.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; and y is 0.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; and R_1 represents aryl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; and R_1 represents aryl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; R_1 represents aryl; and R_2 represents independently for each occurrence alkyl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; and R_3 represents H.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; and R_4 represents aryl.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; R_4 represents aryl; and R_5 represents independently for each occurrence H.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; R_4 represents aryl; R_5 represents independently for each occurrence H; and R_6 represents independently for each occurrence H.

In certain embodiments, the formulations of the present invention comprise a compound represented by **A** and the attendant definitions, wherein m is 2; y is 0; R_1 represents phenyl; R_2 represents independently for each occurrence ethyl; R_3 represents H; R_4 represents phenyl; R_5 represents independently for each occurrence H; and R_6 represents independently for each occurrence H.

In certain embodiments, the present invention relates to the aforementioned formulations and the corresponding attendant definitions, wherein said compound is a single stereoisomer.

In certain embodiments, the present invention relates to a method of treating pain, drug addiction, or tinnitus in a mammal, comprising the step of administering to a mammal with pain, drug addiction, or tinnitus an effective amount of a formulation of the present invention. In certain embodiments of this method, said mammal is a primate, equine, canine or feline. In certain embodiments of this method, said mammal is a human. In certain embodiments of this method, said formulation is administered orally. In certain embodiments of this method, said formulation is administered intravenously. In certain embodiments of this method, said formulation is administered sublingually. In certain embodiments of this method, said formulation is administered ocularly.

In vivo *Activity Assays*

Various experimental procedures, well known in the art, are useful in the present invention to assess the analgesic effect of compounds, such as the "tail flick" and "hot

plate" tests. The "tail flick" test can be performed by applying a noxious thermal stimulus to the rat's tail and determining the time until the nociceptive tail flick occurs. Analgesia is demonstrated by an increase in time to occurrence of a tail flick response. The "hot plate" test is similarly performed, except that the noxious thermal stimulus is applied to the rat's paws.

An experimental procedure, well known in the art, useful in the present invention to assess the ability of compounds to cause respiratory depression is to monitor blood gases. This method employees measuring the partial pressures of oxygen and carbon dioxide in blood samples taken from animals following compound administration. A decrease in the partial pressures of oxygen and an increase in the partial pressure of carbon dioxide may be indicative of respiratory depression.

An experimental procedure, well known in the art, useful in the present invention to assess the ability of compounds to cause inhibition of gastrointestinal motility is the "charcoal meal test". This method measures the propulsion of intestinal contents following administration of test compounds. A decrease in the propulsion of intestinal contents may be indicative of inhibition of gastrointestinal motility.

Various experimental procedures, well known in the art, are useful in the present invention to assess the ability of compounds to cause tolerance. Tolerance can be defined as a condition characterized by unresponsiveness or decreased responsiveness following prolonged or multiple exposure to a compound compared to the responsiveness demonstrated upon initial exposure.

Various experimental procedures, well known in the art, are useful in the present invention to assess the ability of compounds to cause physical dependence. In the present invention, the ability of test compounds to cause physical dependence was accessed by giving animals escalating doses of test compounds for five days. After the final dose the animals were given naloxone, an opioid antagonist and observed for behavioral signs of dependence, such as vertical jumping.

Pharmaceutical Formulations

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

Formulations of the present invention may be based in part on liposomes. Liposomes consist of a phospholipid bilayer which forms a shell around an aqueous core. Methods for preparing liposomes for administration to a patient are known to those skilled in the art; for example, U.S. Pat. No. 4,798,734 describes methods for encapsulation of biological materials in liposomes. The biological material is dissolved in a aqueous solution, and the appropriate phospholipids and lipids are added, along with surfactants if required. The material is then dialyzed or sonicated, as necessary. A review of known methods is presented by G. Gregoriadis, Chapter 14 ("Liposomes"), in Drug Carriers in Biology and Medicine, pp. 287-341 (Academic Press, 1979).

Formulations of the present invention may be based in part on polymeric microparticles. Microspheres formed of polymers or proteins are also well known to those skilled in the art, and can be tailored for passage through the gastrointestinal tract, as described in U.S. Pat. Nos. 4,906,474, 4,925,673, and 3,625,214, for example. There are a number of well-known methods, including solvent evaporation and coacervation/phase separation, for preparing microspheres. Bioerodible microspheres can be prepared using any of the methods developed for making microspheres for drug delivery, as described, for example, by Mathiowitz et al., J. Appl. Polymer Sci. 35, 755-

774(1988), and P. Deasy, in Microencapsulation and Related Drug Processes, pp. 61-193, (Dekker, 1984), the teachings of which are incorporated herein. The selection of a method depends on the drug properties and choice of polymer, as well as the size, external morphology, and degree of crystallinity desired, as discussed, for example, by Benita et al., J. Pharm. Sci. 73, 1721-1724 (1984), Jalil and Nixon, J. Microencapsulation, 7, 297-325(1990), and Mathiowitz et al., Scanning Microscopy 4, 329-340(1990), the teachings of which are incorporated herein.

In solvent evaporation, described, for example, in Mathiowitz et al., (1990), Benita, and U.S. Pat. No. 4,272,398 to Jaffe, the polymer is dissolved in a volatile organic solvent. The drug, either in soluble or particulate form, is added to the polymer solution and the mixture is suspended in an aqueous phase containing a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporates, leaving solid microspheres. Microspheres of various sizes (1-1000 microns) and morphologies may be obtained by this method, which is useful for non-labile polymers.

Coacervation/phase separation techniques have been used to encapsulate both solid and liquid core materials with various polymer coatings. U.S. Pat. Nos. 2,730,456, 2,730,457, and 2,800,457 to Green and Schleichter, describe gelatin and gelatin-acacia (gum arabic) coating systems, for example. Simple coacervation employs a single colloid (e.g. gelatin in water) and involves the removal of the associated water from around the dispersed colloid by agents with a higher affinity for water, such as alcohols and salts. Complex coacervation employs more than one colloid, and the separation proceeds mainly by charge neutralization of the colloids carrying opposite charges rather than by dehydration. Coacervation may also be induced using nonaqueous vehicles, as described in Nakano et al., Int. J. Pharm, 4, 29-298(1980), for example.

Hydrogel microspheres made of gel-type polymers such as alginate or polyphosphazenes or other dicarboxylic polymers can be prepared by dissolving the polymer in an aqueous solution, suspending the material to be incorporated into the mixture, and extruding the polymer mixture through a microdroplet forming device, equipped with a nitrogen gas jet. The resulting microspheres fall into a slowly stirring,

ionic hardening bath, as illustrated, for example, by Salib, et al., Pharmazeutische Industrie 40-11A, 1230(1978), the teachings of which are incorporated herein. The advantage of this system is the ability to further modify the surface of the microspheres by coating them with polycationic polymers (such as polylysine) after fabrication, as described, for example, by Lim et al, J. Pharm Sci. 70, 351-354(1981). The microsphere particle size depends upon the extruder size as well as the polymer and gas flow rates.

Examples of polymers that can be used include polyamides, polycarbonates, polyalkylenes and derivatives thereof including, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polymers of acrylic and methacrylic esters, including poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate), polyvinyl polymers including polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, poly(vinyl acetate), and polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, celluloses including alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, and cellulose sulphate sodium salt, polypropylene, polyethylenes including poly(ethylene glycol), poly(ethylene oxide), and poly(ethylene terephthalate), and polystyrene.

Examples of biodegradable polymers include synthetic polymers such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butic acid), poly(valeric acid), and poly(lactide-cocaprolactone), and natural polymers such as alginate and other polysaccharides including dextran and cellulose, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In

general, these materials degrade either by enzymatic hydrolysis or exposure to water in vivo, by surface or bulk erosion.

Bioadhesive polymers of particular interest include bioerodible hydrogels described by H. S. Sawhney, C. P. Pathak and J. A. Hubbell in Macromolecules, 1993, 26, 581-587, the teachings of which are incorporated herein, polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

A diluent used in a composition of the present invention can be one or more compounds which are capable of densifying the active principle to give the desired mass. The preferred diluents are mineral phosphates such as calcium phosphates; sugars such as hydrated or anhydrous lactose, or mannitol; and cellulose or cellulose derivatives, for example microcrystalline cellulose, starch, corn starch or pregelatinized starch. Very particularly preferred diluents are lactose monohydrate, mannitol, microcrystalline cellulose and corn starch, used by themselves or in a mixture, for example a mixture of lactose monohydrate and corn starch or a mixture of lactose monohydrate, corn starch and microcrystalline cellulose.

A binder employed in a composition of the present invention can be one or more compounds which are capable of densifying a compound of formula (I), converting it to coarser and denser particles with better flow properties. The preferred binders are alginic acid or sodium alginate; cellulose and cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose or methyl cellulose, gelatin; acrylic acid polymers; and povidone, for example povidone K-30; hydroxypropyl methyl cellulose and povidone K-30 are very particularly preferred binders.

A disintegrating agent employed in a composition of the present invention can be one or more compounds which facilitate the disintegration of the prepared formulation when it is placed in an aqueous medium. The preferred disintegrating agents are cellulose

or cellulose derivatives such as sodium carboxymethyl cellulose, crosslinked sodium carboxymethyl cellulose, micro-crystalline cellulose, cellulose powder, crospovidone; pregelatinized starch, sodium starch glyconate, sodium carboxymethyl starch, or starch. Crospovidone, crosslinked sodium carboxymethyl cellulose and sodium carboxymethyl starch are preferred disintegrating agents.

An antiadhesive employed in a composition of the present invention can be one or more compounds which are capable of reducing the sticky character of the formulation, for example of preventing adhesion to metal surfaces. The preferred antiadhesives are compounds containing silicon, for example silica or talcum.

A flow promoter employed in a composition of the present invention can be one or more compounds which are capable of facilitating the flow of the prepared formulation. The preferred flow promoters are compounds containing silicon, for example anhydrous colloidal silica or precipitated silica.

A lubricant employed in a composition of the present invention can be one or more compounds which are capable of preventing the problems associated with the preparation of dry forms, such as the sticking and/or seizing problems which occur in the machines during compression or filling. The preferred lubricants are fatty acids or fatty acid derivatives such as calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium laurylsulfate, sodium stearylfumarate, zinc stearate or stearic acid; hydrogenated vegetable oils, for example hydrogenated castor oil; polyalkylene glycols or polyethylene glycol; sodium benzoate; or talcum. Magnesium stearate or sodium stearylfumarate is preferred according to the present invention.

A color employed in a formulation of the present invention can be one or more compounds which are capable of imparting the desired color to the prepared formulation. The addition of a color can serve for example to differentiate between formulations containing different doses of active principle. The preferred colors are iron oxides.

As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic,

inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19)

The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like.

Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*)

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound selected from the group consisting of fentanyl and its congeners as defined *supra*. In certain embodiments, an aforementioned formulation renders orally

bioavailable a compound selected from the group consisting of fentanyl and its congeners as defined *supra*.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may

also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions,

syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials,

such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration

route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or

amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the subject compounds, as described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous

solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin, lungs, or oral cavity; or (4) intravaginally or intravectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other pharmaceuticals.

The term "treatment" is intended to encompass also prophylaxis, therapy and cure.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

The compound of the invention can be administered as such or in admixtures with pharmaceutically acceptable carriers and can also be administered in conjunction with antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy, thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutical effects of the first administered one is not entirely disappeared when the subsequent is administered.

The addition of the active compound of the invention to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compound in an effective amount and incorporating the premix into the complete ration.

Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed. The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied Animal Nutrition", W.H. Freedman and CO., San Francisco, U.S.A., 1969 or "Livestock Feeds and Feeding" O and B books, Corvallis, Ore., U.S.A., 1977).

Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

Orally Bioavailable Formulation of Fentanyl

Male Sprague-Dawley rats (150-200 grams), were fasted for 16 hours, but were allowed free access to water, were identified, weighed, and randomly assigned to a treatment group. An oral dose of drug (or vehicle) was given via a gavage needle, and post-drug tail flick latencies were subsequently determined at 10, 20, 30, 45, and 60 minutes post-dosing, to determine the degree of analgesia. A cut-off TF latency of 10 seconds was employed to prevent tissue damage. Fentanyl was dissolved in saline or 10% hydroxypropyl-β-cyclodextrin (10% β-HPCD) or 10% hydroxypropyl-γ-cyclodextrin (10% γ-HPCD), and administered in a volume of 0.5 mL. All fentanyl doses are expressed as weight of free base. The latency to tail-flick of the fentanyl-treated animals was recorded at each of the time points described above, and compared with the latencies observed at coincident time points of the vehicle groups.

Six animals were tested for analgesia (tail flick latency) with orally administered formulations (saline or 10% β-HPCD or 10% γ-HPCD) of fentanyl (0.050 mg/kg) for each of the following time points: 0 min (pre-dose), 15 min, 30 min, 45 min, and 60 minutes post dosing. The results are presented herein.

Time (min.)	**0** (pre dose)	**+15** (after dose)	**+30** (after dose)	**+45** (after dose)	**+60** (after dose)
10% β-HPCD Formulation (MPE %)[a]	**0**	**99**	**52**	**25**	**8**
10% γ-HPCD Formulation (MPE %)[a]	**0**	**49**	**65**	**67**	**55**
Saline Formulation (% MPE)	**0**	**40**	**19**	**33**	**53**

[a] MPE = Maximum Possible Effect

Incorporation By Reference

All of the patents and publications cited herein are hereby incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.